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REVIEW ARTICLE

Optimal Dosages for Melatonin Supplementation Therapy in Older Adults: A Systematic Review of Current Literature

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Abstract
Background Melatonin is a hormone that regulates circadian rhythm, and its levels decline with age. As melatonin levels decrease, older adults are prone to develop disorders related to an altered circadian rhythm. The effective dose of melatonin supplementation in these disorders remains unclear.
Objectives Our objective was to define the optimal dosage of exogenous melatonin administration in disorders related to altered melatonin levels in older adults aged 55 years and above by determining the dose-response effect of exogenous administered melatonin on endogenous levels.
Methods We conducted a systematic review through PubMed/MEDLINE and Embase, both from 1980 until November 2013. Included articles studied the effect of exogenous melatonin administration on endogenous melatonin levels in either serum, urine, or saliva in humans aged 55 years and above.
Results We included 16 articles, nine of which were randomized controlled trials (RCTs). The mean age varied from 55.3 to 77.6 years. Melatonin dosage varied from 0.1 mg to 50 mg/kg and was administered orally in all studies. Pre- and post-intervention levels revealed a significant elevation of the post-intervention melatonin levels in a dose-dependent fashion. The maximum concentrations measured in serum and urine were all elevated compared with placebo, and a higher elevation in older adults than in younger adults was demonstrated. Even though there were no differences between times to reach maximum concentration in serum and urine, melatonin levels with higher doses were maintained longer above a certain threshold than were lower doses.
Conclusion In older adults, we advise the use of the lowest possible dose of immediate-release formulation melatonin to best mimic the normal physiological circadian rhythm of melatonin and to avoid prolonged, supra-physiological blood levels.

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1 Introduction

Melatonin is a lipophilic hormone produced in the pineal gland, and its production/synthesis is controlled by the suprachiasmatic nucleus (SCN). Melatonin is a regulator of the circadian rhythm, as its production by the pineal gland is suppressed by light and controlled by the SCN, resulting in low concentrations during daytime. During evening hours, serum melatonin levels start to rise, reaching peak concentration around 2–4 am, after which melatonin levels decline again until reaching low daytime levels [1]. In healthy subjects, the average peak of melatonin in serum at night reaches values around 60 pg/ml, gradually declining to levels as low as <10 pg/ml during daytime [1, 2]. It is known that melatonin levels decline in aging adults [3, 4], as melatonin is subject both to altered hormone regulation due to changes in renal and hepatic clearance and to changes in body composition [5]. In addition, mean levels of excretion

are especially low in patients with chronic medical problems, implying that older adults with higher co-morbidity might suffer more from inadequate melatonin levels [6].

As melatonin levels decrease with age, their secretion patterns also alter [4, 7]. It is assumed that older adults are prone to develop disorders that are related to an altered circadian rhythm, such as sleeping disorders [8, 9], disorders of cognitive functioning [10–12], and delirium [13–15]. These previous investigations have shown that administration of exogenous melatonin had beneficial effects. Melatonin mainly synchronizes the sleep–wake cycle by advancing the oscillatory activity of the major circadian pacemaker and restores the circadian secretion pattern and endogenous levels of melatonin [16]. Efficacy of administered melatonin in adults appears to be dependent on the magnitude of the dose and the time of administration [17]. The appropriate timing of exogenous melatonin is widely investigated by its phase response curve (PRC) [18–22]. In this response curve, dim light melatonin onset (DLMO), the time of day when melatonin in dim light conditions starts to rise, can be used to determine the phase shift in disorders related to altered melatonin levels and altered circadian rhythm [23–25]. It is supposed that melatonin administered in the afternoon or early evening, prior to the normal onset of nocturnal melatonin production, can restore disorders related to an altered circadian rhythm [16].

While adequate timing of melatonin administration is investigated, the effective dose of melatonin, especially in older adults, remains unclear [25]. Many studies have investigated pharmacokinetics in younger adults [16, 17, 26–30], but only a few have studied older adults [5, 31]. Melatonin-replacement therapy that mimics normal endogenous melatonin levels might correct a relative melatonin deficiency [32]; though bioavailability might be highly variable between individuals, as exogenous melatonin is subject to an extensive first-pass effect in the liver [33]. Multiple different doses of melatonin are currently used, and studies determining the correct dosage of melatonin remain scarce.

We systematically reviewed the literature to define the optimal dosage of exogenous melatonin administration in older adults with disorders related to altered melatonin levels. Determination of the dose-response effect of exogenous administered melatonin on the endogenous levels of melatonin in older adults aged 55 years and above is described.

2 Methods

2.1 Search Strategy

A systematic search of the literature was conducted in PubMed/MEDLINE and Embase from 1980 until November 2013. We used the following strategy:

1. Melatonin [medical subject heading (MeSH)] OR melatonin*[tiab]
2. (Endogenous[tiab] OR exogenous[tiab]) OR (urine [MeSH] OR "urine"[Subheading] OR urine[tiab]) OR ("Saliva"[MeSH] OR saliva[tiab]) OR ("Serum"[MeSH] OR serum[tiab]) OR ("Blood"[MeSH] OR "blood"[Subheading] OR blood[tiab])
3. (elder*[tiab] OR geriatric[tiab] OR aging[tiab] OR aged[MeSH] OR older[tiab] OR oldest[tiab])
4. animals[MeSH] not humans[MeSH]
5. 1 AND 2 AND 3 NOT 4

Reviews and meta-analyses that met the inclusion criteria were used for cross-referencing.

2.2 Selection Procedure

Articles needed to primarily or secondarily examine the effect of exogenous melatonin administration on endogenous melatonin levels measured by either melatonin in serum, melatonin in saliva or 6-hydroxymelatonin sulphate (6SMT) in urine, melatonin's main metabolite. Articles based on humans aged 55 years and above or with a median age above 55 years, or articles where sub-analysis was provided in older adults were included.

Treatment could involve melatonin itself, melatonin agonists (ramelteon, tasimelteon, or Circadin®), or melatonin analogs (B-methyl-6-chloromelatonin). Treatment with agomelatine, a melatonin plus serotonin agonist was excluded. Articles only measuring endogenous levels without administration of melatonin were also excluded.

We included all prospective clinical studies, mainly randomized controlled trials (RCTs) and case series. No restrictions were placed on language. First selection was based on title only. Second, abstracts and, if needed, full texts were screened.

3 Results

The combination of search terms yielded 737 hits in PubMed/MEDLINE. An additional search through Embase did not reveal any additional relevant papers. Figure 1 describes the selection procedure. After detailed assessment, 16 articles on the direct dose-response relation of exogenous melatonin on endogenous melatonin, measured either in serum or saliva, were selected [2, 5, 31–44].

Baseline characteristics of the included studies are outlined in Table 1. Nine of the 16 studies were RCTs, two of which were conducted in a cross-over design. The mean age of the patients within the studies varied from 55.3 to 77.6 years.

Designs of the included studies are summarized in Table 2, revealing melatonin dosage, route and time of

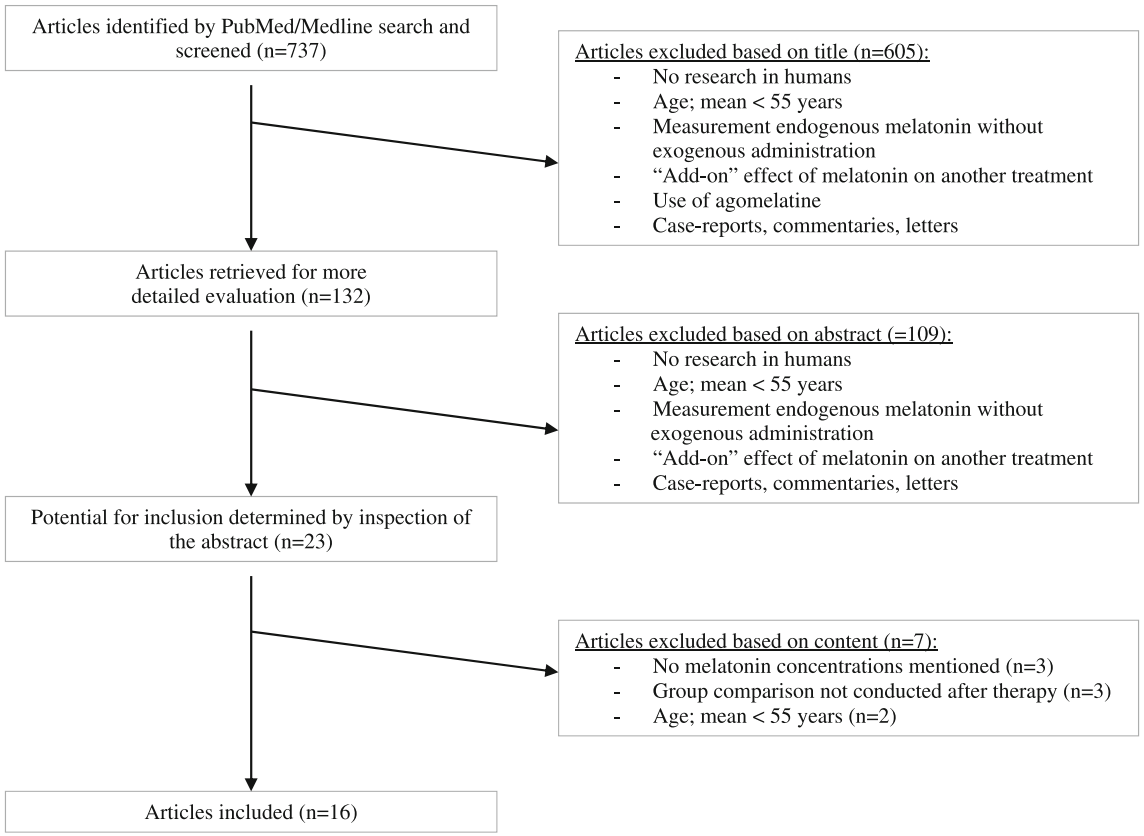

Fig. 1 Flow diagram of search strategy and study selection for melatonin's direct dose-response relation

administration, treatment duration, time and amount of samples taken, and medium in which melatonin was measured. Melatonin dosage varied from 0.1 mg to 50 mg/kg, and all studies used melatonin as treatment, except for one RCT that used ramelteon 18 mg, a melatonin agonist [36]. Melatonin was administered orally in all studies, mainly in capsules, but through a nasal gastric tube (NGT) in three studies [2, 33, 41], as oral liquid in one study [34], and via transbuccal patches in one study [35].

Treatment duration varied from a single dose up to daily melatonin supplementation for 6 months. The time of administration was mainly at fixed times in the evening or at a standardized time before each individual's bedtime, except for in three studies [31, 33, 36]. In two of these studies, melatonin was administered in the morning; in another study, melatonin was administered after intubation for general anesthesia.

The effects of exogenous melatonin administration on endogenous melatonin levels and other pharmacokinetics are presented in Table 3. Melatonin concentrations were all converted into picogram/milliliter (pg/ml). Of the 16 studies, 11 measured baseline endogenous melatonin levels all in serum before treatment, which were all comparable to reference values. Eleven studies measured post-treatment melatonin levels in either serum or urine, while only eight studies compared both pre- and post-intervention levels. All eight revealed a significant elevation of the post-intervention melatonin levels compared with pre-treatment levels in a dose-dependent fashion. The other three studies that only measured post-treatment values compared melatonin levels between melatonin supplementation and placebo, all showing an increase in relation to placebo after supplementation [33, 35, 40].

Seven studies examined maximum concentrations (C_{max}), all in serum and one [31] also in saliva. All concentrations were elevated compared with placebo. Two of these studies also compared maximum concentrations between older and younger adults, revealing a higher elevation in older subjects [31, 36]. Three studies administered different doses of melatonin, leading to a significant dose-dependent elevation of C_{max} reached [5, 32, 44]. Time to reach C_{max} (t_{max}) was determined in six studies and did not differ between treatment and placebo groups. Another two studies compared t_{max} in different doses, showing no difference [5, 32]. Also, t_{max} as compared in younger and older adults did not differ [36]. In addition, another study reported a longer t_{max} in saliva compared with serum in healthy adults [31].

Three studies examined the duration for which melatonin levels remained above a set threshold. Two of these

Table 1 Baseline characteristics of included studies

References	Study design	Study population	Sample size	Sex (% M)	Age, years[a]
Bourne et al. [34]	RCT	Tracheotomized pts	24	45.8	58.7 ± 12.5
Dawson et al. [35]	RCT, crossover	Elderly aged ≥55 with sleep maintenance insomnia	12	NM	65.7 ± 1.7
Gooneratne et al. [5]	RCT	Older adults with insomnia	27	0 low dose 11.1 high dose	75.1 ± 6.2
Greenblatt et al. [36]	RCT, crossover	Healthy adults	48	50	70 ± 0.9
Hughes et al. [37]	RCT, crossover	Insomniacs aged 55–80	14	35.7	70.3 ± 1.9
Ibrahim et al. [2]	RCT	Tracheotomized ICU pts	32	59.4	63 (54–72)
Kedziora-Kornatowska et al. [38]	Case series	Elderly with hypertension	17	NM	77.6 ± 2.7
Kedziora- Kornatowska et al. [39]	Case series	Elderly with non-insulin-dependent DM	30	43.3	77 ± 8.7
Lemoine et al. [40]	Open-label	Adults with primary insomnia	112	31	55.3 ± 13
van Marke de Lumen et al. [43]	Case series	Arterial hypertension	24	NM	76.7 ± 10
Mistraletti et al. [41]	Case series	ICU pts with mechanical ventilation	12	83.3	I: 62 (58–71) II: 74 (56–81)
Nickkholgh et al. [33]	RCT; pilot study	Elective major partial liver resection (≥3 liver segments) for neoplasms	50	58.3	59 ± 10
Shah et al. [32]	Open-label, crossover study	Healthy subjects without sleep disorders	12	50	60–73
Sugaya et al. [42]	RCT (unblinded)	Elderly with nocturia	42	59.5	73 ± 7
Zhdanova et al. [31]	Case series	Healthy young and older adults	20	50	59 ± 10
Zhdanova et al. [44]	RCT	Older adults aged ≥50	30	NM	NM

DM diabetes mellitus, *ICU* intensive care unit, *M* male, *NM* not mentioned, *pts* patients, *RCT* randomized controlled trial, *SD* standard deviation

[a] Data are presented as mean ± SD or median (range)

studies found that melatonin levels in the high-dose groups (respectively, 4.0 and 3.0 mg) were maintained above 50 pg/ml for more than 10 h, longer than in the low-dose groups [5, 44]. The third study could not prove a significant difference for the time melatonin remained above 5 pg/ml in either serum or saliva [31].

Table 4 shows the effect of exogenous melatonin on other outcome measures such as sleep (6 of 16 studies [5, 31, 35, 37, 40, 44]), oxidative stress parameters (three studies [38, 39, 43]), nocturnal urination and quality of life (one study [42]), and core body temperature (one study [35]). The effects of melatonin are mainly positive and only the significant changes within these studies are revealed.

4 Discussion

This systematic review on melatonin dose variation, in which we included a total of nine RCTs, five case-series, and two open-label studies considering adults aged above 55 years, shows various doses of exogenous melatonin administration, varying from 0.1 mg to 50 mg/kg. The effects of exogenous melatonin on pharmacokinetic parameters can be generally stated as dose-dependent, either significant (post-treatment concentration, C_{max}) or non-significant (t_{max}, half-life time [$t_{½}$]).

Levels and rhythm of melatonin secretion varied between older and younger adults as melatonin levels were found to decline with age [3, 4]. The variability in melatonin levels may give rise to problems dosing exogenous melatonin in older adults, but within our review we were able to identify some hallmarks for adequate dosing.

First, we found an elevation of endogenous melatonin after exogenous administration compared with placebo in a dose-dependent manner. Three studies revealed an increase of melatonin levels independent of the administered dosage [5, 32, 44], which implies that administration of 0.5 mg already induces a significant increase of melatonin levels after administration. Furthermore, other studies that used

Table 2 Dosage, route and time of administration, treatment duration, time and amount of samples and medium in which melatonin is measured

References	Melatonin dosage	Administration	Time of administration	Treatment duration	Time of sample collection	Samples (*n*)	Measurement
Bourne et al. [34]	10 mg	Oral liquid	2100 h	4 nights	12 samples at appropriately spaced intervals	12	Serum
Dawson et al. [35]	0.5 mg SR	Transbuccal patch	1900 h	2 sessions 4 nights each	Between 2100–0700 h	2	Urine
Gooneratne et al. [5]	0.4 or 4.0 mg 25 % IR, 75 % CR	Oral	Between 1915 and 2315 h (individual bedtime)	42 days	1200–1800 h 2-hourly; 1800–2400 h every 30 min; 0100–1200 h 1-hourly	28	Serum
Greenblatt et al. [36]	18 mg (ramelteon)	Oral	90 min after standardized breakfast	Single dose	Post-dosage 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, and 24 h. Urine: 0–4, 4–8, 8–12, and 12–24 h	17 4	Serum and urine
Hughes et al. [37]	Early 0.5 mg IR Continuous 0.5 mg CR Late 0.5 mg IR	Oral	30 min before bedtime 30 min before bedtime 4 h after bedtime	Four 2-week trials	Pre-treatment: 2400 h hourly and half hourly from 1800–2400 h; Day 14: 30 min before and after dose, hourly overnight	30 Not mentioned	Serum
Ibrahim et al. [2]	3 mg	NGT; liquid	2200 h	Minimum of 48 h	Days 1 and 3 at 2130 (pre-dose) and 2330 h (post-dose)	4	Serum
Kedziora-Kornatowska et al. [38]	5 mg	Oral	1 h before expected bedtime	30 days	Before treatment and after 15 and 30 days at 2000 h	3	Serum
Kedziora-Kornatowska et al. [39]	5 mg	Oral	1 h before sleep	30 days	Before treatment and after 30 days at 2000 h	2	Serum
Lemoine et al. [40]	2 mg PR	Oral	1–2 h before bedtime (preferably 2100–2200 h)	6 months	Between 0800–2000 h and 2000–0800 h	2	6-SMT urine
van Marke de Lumen et al. [43]	5 mg	Oral	1 h before sleep	30 days	Before treatment and after 30 days 2000 h	2	Serum
Mistraletti et al. [41]	3 mg	NGT; crushed and mixed with water	Just after 2000 h	Single dose	I: 2000, 2045, 2130, 2400, 0300, 0600, 1400 and 2000 h II: 2000, 2005, 2010, 2020, 2030 and 2045 h	I: 8 before and 8 after administration II: 6 before and 6 after administration	Serum
Nickkholgh et al. [33]	50 mg/kg BW	NGT; dissolved in milk	After intubation for general anesthesia	Single dose	Before and 2 and 4 h after administration	3	Serum

Table 2 continued

References	Melatonin dosage	Administration	Time of administration	Treatment duration	Time of sample collection	Samples (*n*)	Measurement
Shah et al. [32]	1 × 110 or 4 × 110 μg CR (OROS)	Oral	2100 h	4 weeks	Baseline: 1800, 2100, 2130 h and from 2200–0900 hourly Day 1 and 15: 2130 h and every hour until 0900 h; Urine: overnight portion from 2100–0900 h	15 26 1	Serum and urine
Sugaya et al. [42]	2 mg	Oral	At bedtime	4 weeks	1000–1200 h at baseline and after 4 weeks	4	Serum
Zhdanova et al. [31]	0.3 mg	Oral	1100 h	Single dose	Every 30 min between 0900–1800 h	19	Serum and saliva
Zhdanova et al. [44]	0.1, 0.3, or 3.0 mg	Oral	Half h before each subject's fixed bedtime	7 weeks	Second inpatient night from 1700 h 15–60 min for 24 h	Not mentioned	Serum

BW body weight, *Continuous* 0.5 mg CR taken 30 min before bedtime and placebo taken 4 h after bedtime, *CR* controlled release, *Early* 0.5 mg IR taken 30 min before bedtime and placebo taken 4 h after bedtime, *IR* immediate release, *NGT* nasal gastric tube, *PR* prolonged release, *SR* sustained release, *Late* placebo taken 30 min before bedtime and 0.5 mg IR taken 4 h after bedtime, *OROS* an oral osmotic system for controlled drug delivery, *6-SMT* 6-hydroxymelatonin sulphate (melatonin's main metabolite in urine)

Continuous = 0.5 mg CR taken 30 min before bedtime and placebo taken 4 h after bedtime; Early = 0.5 mg IR taken 30 min before bedtime and placebo taken 4 h after bedtime; Late = placebo taken 30 min before bedtime and 0.5 mg IR taken 4 h after bedtime

Table 3 Effects of exogenous melatonin on endogenous melatonin parameters

References	Pre-tx concentrations (pg/mL)	Pre-tx measurement	Post-tx concentration (pg/mL)	Post-tx measurement	C_{max} (pg/ml)	t_{max}	$t_{½}$	Prolongation of elevated levels (pg/ml)
Bourne et al. [34]					14.974 (3.200)	0.5 h (0)	1.47 h (0.28)	
Dawson et al. [35]			45.1 ± 3.8	Urine				
Gooneratne et al. [5]	5.8 (2–9.5)	Serum			405	Low: 1.3 ± 0.19 h	1.8 h	6.4 h > 50
	Peak 46.7 (23.6–118)				3,999	High: 1.5 ± 0.24 h	2.1 h	10 h > 50
Greenblatt et al. [36]					6,900 ± 1,600	Young: 1.6 h (±0.1)	1.3 h (±0.1)	
					11,600 ± 2,800[a]	Elderly: 1.4 h (±0.1)	1.9 h (±0.1)[b]	
Hughes et al. [37]	4.7–100.1	Serum	Early 838.7 ± 164.1 (range 145.7–2,345.0) Late 703.8 ± 154.1 (range 159.4–2,117.0) Continuous 394.5 ± 81.3 (range 135.5–1,373.0)	Serum			42.42 ± 2.93 min (IR)	
Ibrahim et al. [2]	4.8 (95 % CI 2.4–7.5)	Serum	3,543 (1,533–8,100)	Serum				
Kedziora- Kornatowska et al. [38]	7.3 ± 1.4	Serum	15 days: 20.5 ± 5.6 30 days: 17.2 ± 2.8	Serum				
Kedziora- Kornatowska et al. [39]	NIDDM 20.8 ± 5.5; healthy adults 51.1 ± 7.0	Serum	NIDDM 35.3 ± 11.76	Serum				
Lemoine et al. [40]			15,300 ± 7,700 pg (4–30)	6-SMT urine				
van Marke de Lumen et al. [43]	7.65 ± 4.6	Serum	19.57 ± 11.7 pg/ml	Serum				
Mistraletti et al. [41]	Cohort I (melatonin profile measured for 24 h): 3–20 Cohort II (melatonin profile measured the 1st h): 3–11	Serum	Cohort I: 2045 h 9,588 (5,874–9,695) 2130 h 6,531 (4,397–6,641) 2400 h 1,616 (1,248–1,735) 0300 h 439 (274–1311) 0600 h 138 (50–251) 1400 h 48 (16–118) 2000 h 21 (9–82) Cohort II (first h profile): 2005 h 4,691 (4,026–4,997) 2010 h 6,168 (3,627–12,074) 2020 h 5,483 (3,148–11,138) 2030 h 2,641 (1,498–5,310) 2045 h 1,281 (889–6,475)	Serum	11,039.84	0.27 h		
Nickkholgh et al. [33]			1,142,800 ± 7,200 (4,300–1,474,000)	Serum	14,740,000			
Shah et al. [32]	Day −1 36.1 ± 20.3	Serum			56.9 ± 50.8	1 × 110: 5.8 ± 1.6 h		
	Day 14 34.4 ± 20.0				179 ± 97.2[c]	4 × 110: 5.5 ± 1.0 h		
Sugaya et al. [42]	Melatonin 5.6 ± 5.2	Serum	87.2 ± 71.7 pg/ml[d]	Serum				
	Rilmazafone 6.3 ± 3.0		6.4 ± 4.9 pg/ml					

Table 3 continued

References	Pre-tx concentrations (pg/mL)	Pre-tx measurement	Post-tx concentration (pg/mL)	Post-tx measurement	C_{max} (pg/ml)	t_{max}	$t_{½}$	Prolongation of elevated levels (pg/ml)
Zhdanova et al. [31]	49.4 ± 38.1	Serum			254.9 ± 145.7	Serum: 45 ± 6.7 min		6.6 ± 0.24 h > 5
					74.4 ± 43.6	Saliva: 81 ± 6.4 min[e]		4.4 ± 0.24 h > 5
Zhdanova et al. [44]	25 (17–39)	Serum	0.1 mg: 84 (59–120)	Serum				>10 h > 50
			0.3 mg: 220 (124–299)					
			3.0 mg: 1370 (957–2440)					

Pre- and post-tx concentrations are either defined as mean ± SD or median with or without range. Values of melatonin concentrations are converted into picogram/milliliter (pg/mL)

CI confidence interval, C_{max} maximum reached concentration, *IR* immediate release, *NIDDM* non-insulin dependent diabetic mellitus, t_{max} time to reach maximum concentration, *tx* treatment, $t_{½}$ half-life time, *6-SMT* 6-hydroxymelatonin sulphate (melatonin's main metabolite in urine)

[a] Significant difference ($p < 0.05$) between younger and older adults

[b] Significant ($p < 0.001$) difference between younger and older adults

[c] Significant ($p < 0.05$) difference between the doses

[d] Significant difference ($p < 0.01$) between the melatonin and the rilmazafone conditions

[e] Significant ($p < 0.001$) difference between serum and saliva

even lower doses showed significant increases in melatonin levels [5, 31, 37, 44]. In younger adults, it is amply proven that low exogenous doses of melatonin, even above 0.3 mg, produce supra-physiological levels [16, 20–22, 26–30, 35] as well as in older adults [33]. When melatonin is administered in older adults, a higher variance of serum melatonin levels than in younger subjects can seen (76–486 vs. 142–205 pg/ml in the younger group; $p < 0.0001$) [31]. Besides this, the maximum concentration reached after melatonin administration has a tendency to be higher in older age [31, 45, 46], and the increment is also greater and more variable amongst people aged over 48 years [31]. Our review round a small but significant relation between age and pharmacokinetic parameters (difference in C_{max} and $t_{½}$) [36], but in contrast, other studies failed to find such a relation between higher age and $t_{½}$ [5, 32].

Second, we also demonstrated that higher doses of exogenous melatonin cause prolongation of elevated melatonin levels. Gooneratne et al. [5] showed that a higher dose in a 75 % sustained-release formulation (4 mg) compared with a lower dose (0.4 mg) caused significant prolongation of elevated melatonin levels lasting throughout the morning hours and during the day. Also, Zhdanova et al. [44] found that melatonin levels in the high-dose group (3 mg) were maintained above a set threshold for longer than in the low-dose groups (0.1 and 0.3 mg). This implies that a higher maximum dose carries the risk of prolongation of supra-physiological levels in older adults throughout the next day. This might cause problems with side effects like drowsiness, somnolence, or unsteady feeling when waking up, despite melatonin's low toxicity [30, 33, 36, 42].

The included studies also investigated additional effects of exogenous melatonin administration on other outcomes such as sleep and core body temperature. Exogenous melatonin had a positive effect on sleep parameters [5, 31, 35, 37, 40, 44]. Some studies showed that with higher doses and prolongation of supra-physiological levels, melatonin loses its effectiveness on sleep parameters, and with lower doses it can regain its effectiveness [25, 31, 44, 47]. In addition to this, higher doses are more influential on body temperature [35]. But within these results, differences were found with a sustained-release melatonin dose of 0.5 mg, which either lowered core body temperature or mimicked the normal endogenous melatonin profile and did not intervene with normal circadian temperature rhythm [35, 37].

Although we found some interesting results, the quality of the studies varied greatly. First, the types of studies differed, allowing no adequate comparison. Second, baseline characteristics included relatively small sample sizes, the percentage of men between the studies varied greatly and, although median ages were comparable, the oldest old

Table 4 Effect of exogenous melatonin on other outcome measures

References	Other outcomes
Dawson et al. [35]	Early morning awake time ↓; WASO ↓; body temperature ↓
Gooneratne et al. [5]	PSQI ↑
Hughes et al. [37]	Latency to 10 min of persistent sleep ↓ (early, continuous); sleep latencies ↓ (early, late)
Kedziora-Kornatowska et al. [38]	MDA ↓; SOD-1 ↑; CAT ↑
Kedziora-Kornatowska et al. [39]	MDA ↓; serum oxidase activity ↓; SOD-1 ↑
Lemoine et al. [40]	% nights scored good ↑; % good mood ↑
van Marke de Lumen et al. [43]	MDA ↓; SOD-1 ↑
Sugaya et al. [42]	Nocturnal urinations ↓; QoL ↑
Zhdanova et al. [31]	Sleep onset ↑ in young vs. adults; sleep offset ↑ in young vs. adults
Zhdanova et al. [44]	Sleep efficiency ↑ in all three doses

CAT catalase, *MDA* malondialdehyde concentration, *PSQI* Pittsburgh Sleep Quality Index, *QoL* quality of life, *SOD-1* Cu–Zn superoxide dismutase, *WASO* wake after sleep onset, ↓ indicates significant decrease of outcome measure, ↑ indicates significant increase of outcome measure

were not included. Third, various doses and formulations of melatonin were used and treatment durations varied widely. In accordance to this, only eight studies compared pre- with post-treatment levels. Also, different pharmacokinetic parameters were used, leading to some non-comparable, individual outcomes. Additionally, some papers reported only a single post-treatment melatonin level without other pharmacokinetic and -dynamic parameters.

5 Conclusion

The best applicable dosage for melatonin for older adults still cannot be adequately determined, as endogenous melatonin levels are subject to altered pharmacokinetics and -dynamics. This causes higher intra-individual variability, higher maximum concentrations by a greater and more variable increment, and, thereby, the risk of prolonged and elevated endogenous melatonin levels after exogenous melatonin administration in older adults. In accordance, endogenous melatonin levels need to remain within the normal physiological range. This suggests that supplementation needs to be as low as possible, as lower doses also seem more effective on other outcome measures, such as sleep, and do not interfere with core body temperature. While controlled-release formulations most closely mimic natural physiological melatonin levels, they also cause prolongation of elevated melatonin levels in older adults and are therefore not advisable.

Therefore, we advise the use of the lowest possible dose of immediate-release formulation melatonin in older adults, varying from 0.3 mg (which is already effective) to a maximum of 1 or 2 mg, preferably 1 h before bedtime to best mimic the normal physiological circadian rhythm of melatonin and to avoid prolonged, supra-physiological blood levels.

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